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The effects of atropine on respiratory sinus arrhythmia in asthma

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Heart rate is rhythmically related to respiratory rate, in a phenomenon known as respiratory sinus arrhythmia (RSA). Amplitude of RSA has been found to be an accurate noninvasive measure of vagal tone in the normal population. The purpose of this study was to examine the relationship between RSA and cardiac vagal tone among asthmatics, a group which has been described as having elevated RSA. This was accomplished by examining the effects of atropine on RSA in asthmatics, and comparing the results to those obtained elsewhere among normal subjects. Atropine at a dose of 1 mg/75 kg body weight was administered to 18 asthmatics, and produced decreases in RSA, equivalent to those previously found among normal subjects. The results suggest that the relationship between cardiac vagal tone and RSA is unaffected by the presence of asthma.

Introduction

Heart rate fluctuates cyclically with respiratory rate in a phenomenon known as respiratory sinus arrhythmia (RSA). Amplitude of RSA has been found to be an accurate and noninvasive measure of cardiac vagal tone in the normal population (1–3). Changes in vagus nerve activity induced by pharmacological agents, electrical stimulation, surgery, and various disease processes are all sensitively reflected by RSA (1–3).

However, it is not known whether RSA is a valid measure of cardiac vagal tone among asthmatics, because of the complexity of the interrelationship between breathing and cardiac rhythm. The presence of asthma has been linked to RSA elevations (4), but this does not definitively prove that vagal tone is elevated in asthma, because it remains possible that the respiratory abnormalities accompanying asthma may obscure the relationship between RSA and vagal tone. This study was therefore designed to test the effects of parenteral atropine on RSA amplitude in asthma, and to compare atropine-produced RSA changes among asthmatics with those produced by equivalent doses of atropine given to normal subjects in a previous study (5).

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Methodology

SUBJECTS

Eighteen asthmatic adults between the ages of 18 and 40, ten female and eight male, were studied. The experiment required two sessions, for which subjects were paid a total of $125. Subjects came to the screening session by word of mouth, by advertisement, through private physician referrals, and from the pool of persons who had previously participated in asthma research protocols. The diagnosis of asthma was confirmed by a board certified pulmonary physician (S.H.), after spirometric studies, histories and physical examinations.

The following criteria were all required for participation in the study, unless asthma had previously been confirmed by a methacholine challenge test. A history of recurrent asthma (wheeze which responded to beta-2 aerosol therapy) within the prior 12 months, a prior clinical diagnosis of asthma, and abnormal spirometry (FEV_1<80%, FEF_{50}<60%) with no evidence of restrictive lung disease. Ten subjects had previously, within a year of testing, completed methacholine challenge tests with abnormal results. Two of these subjects were included in the present study despite normal spirometry findings on the day of testing, because the methacholine challenge test is considered to be definitive for detecting asthma (6). Pulmonary function test and methacholine challenge test data are presented in Table 1.

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Table 1 Subject characteristics and individual pulmonary data

Subject no.	Order*	FEV_1				FEF_{50}				MCT Data (PD 20)
		Atropine		Placebo		Atropine		Placebo		
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	
420	p/a	73	74	55	26	98	77	23	6	
435	a/p	34	38	41	45	9	11	14	23	2
436	p/a	51	53	55	43	14	23	17	14	
450	a/p	82	82	80	83	64	67	63	63	4
461	a/p	93	69	59	70	86	45	35	54	2
479	a/p	52	65	69	71	17	31	35	38	
482	p/a	102	99	98	99	71	62	58	63	5
486	a/p	32	31	28	27	11	10	9	9	3
496	p/a	78	81	84	83	41	50	53	50	4
497	a/p	93	102	100	93	55	82	70	65	4
498	p/a	81	86	81	86	43	108	38	42	2
501	a/p	42	46	48	48	11	16	10	11	
503	p/a	46	68	63	66	17	30	30	31	
504	p/a	97	102	98	98	80	126	98	95	5
505	p/a	91	81	79	78	71	56	59	53	5
506	p/a	43	56	44	45	14	26	17	19	
508	p/a	40	53	57	59	15	24	27	27	
525	p/a	20	22	16	17	24	29	12	16	

*The order 'p/a' represents placebo given in the first testing session, and atropine in the second. The order 'a/p' represents the opposite order.

Subjects were excluded for any of the following reasons: a history of chronic bronchitis or sinusitis, history or physical findings consistent with emphysema or non-asthma respiratory disease, a history of smoking cigarettes within the past 2 years, presence of cardiovascular or neurological disease, or psychiatric disorders requiring the administration of psychoactive medication.

Subjects refrained from using bronchodilator medication for 12 h before screening spirometry, and avoided caffeine on the day of testing. Informed consent was obtained at the beginning of the first session, after each subject was provided with written and verbal descriptions of all procedures and all anticipated drug effects. The procedures were approved by the committee for protection of human subjects of Robert Wood Johnson Medical School.

For subjects who had received it, the methacholine challenge test used the five-breath method, following the standard procedures described by Chai, *et al.* (6) Accordingly, subjects were administered increasing doses of methacholine until a 20% decrease in FEV_1 was achieved, to a maximum of nine doses. Subjects who tolerated nine doses of methacholine without a 20% decrement in FEV_1 were excluded from the study, regardless of spirometry results, asthma history, or other findings.

EQUIPMENT

Spirometry was recorded on a water seal spirometer (Collins Pulmonary Testing System DS2). For assessing cardiac vagal tone, electrocardiogram signal (EKG) was amplified on a customized AC amplifier and recorded on a Series 700 Vetter Model A tape recorder. At a later time it was played back through a Delta-Biometrics Vagal Tone Monitor. (This instrument analyses average peak-to-trough amplitude of heart period variability at respiratory frequencies (7). In this study, a frequency range of 0·12–0·40 Hz was used, which corresponds to adult respiratory rhythm. The digital filter was calculated as described by Bohrer and Porges (8). The vagal tone monitor produced the $\hat{V}$ statistic, a measure of RSA amplitude (the $\log_e$ of the average peak-to-trough amplitude in heart period, in ms, for fluctuations occurring in the prescribed frequency band). This statistic was originally described in the patent for the device (9) and has subsequently been described by others in the journal literature (10). The formula and equipment for assessing and computing $\hat{V}$ was derived from studies using cross-spectral analysis to determine the proportion of the periodic fluctuations in heart period that occur within the expected respiratory frequencies for an adult human population.

SETTING AND EXPERIMENTERS

Spirometry testing and the administration of medication were performed by a board certified pulmonary physician. Double-blind procedures were used, such that neither the physician nor the patient was told whether active drug or placebo was being administered in any given session.

GENERAL PROCEDURE FOR THE STUDY

Subjects were seen on two separate occasions, separated by between 2 days and 1 month. The order of placebo/active drug was randomized, using a table of random numbers. Half the subjects were tested with the drug in the first session and half with the placebo. Subjects received the other condition (drug or placebo) in the second session. For each subject, both sessions were held during an afternoon visit at approximately the same time of day, in order to minimize the effects of diurnal variation in asthma.

Upon subjects' arrival, resting EKG was recorded for 5 min. During this procedure, subjects were instructed to sit comfortably in a straight back chair, with eyes closed, and to remain still. Following EKG recording, flow volume loops were obtained using standard technique. Three forced expiratory manoeuvres were performed using maximal effort. If equivalent flow volume curves were achieved (i.e., FEV_1+FVC within 5%) the curve with the highest FEV_1+FVC was chosen for analysis. Subjects were then injected with atropine or placebo, as described below. If equivalent curves were not obtained, additional manoeuvres were done until three equivalent curves were obtained. If equivalent curves could not be obtained, the curve with the highest value of FEV_1+FVC was scored (11).

After the injection, subjects were asked to remain in the waiting room for 30 min. Thereafter, EKG and spirometry tests were administered exactly as described above.

PROCEDURE FOR ADMINISTERING MEDICATION

In each session, subjects received an injection in the deltoid muscle of either atropine sulphate (1 mg/75 kg body weight) or placebo (normal saline). This dose of atropine sulphate has previously been found to produce significant decreases in cardiac vagal tone in a normal population (5). For the placebo condition, the same quantity of normal saline was injected. To preserve double blind conditions, the syringes were filled from identically-appearing vials of atropine sulphate and placebo.

STATISTICAL ANALYSIS

Statistical analysis was performed on a PC-AT computer, utilizing the SAS Version 6.03 software package (12).

Results

Table 1 defines the study group's distribution of asthma severity for each day of testing. On each day, in approximately half the subjects, asthma was moderate (FEV_1=40–60%) or severe (FEV_1<40%). As can be seen in Table 1, some subjects had normal pulmonary function on the day of testing, despite a history of asthma, as defined above.

To determine whether the dose of atropine was sufficient to produce measurable bronchodilation, spirometry data (FEV_1, FEF_{50}, FVC) were submitted to a repeated measures multivariate analysis of variance (MANOVA). The statistical model included one between-groups factor, ORDER of drug administration (atropine in the first session and placebo in the second, versus the opposite order), and two repeated measures, DRUG (*vs.* placebo) and PRE/POST (i.e. before drug administration *vs.* afterward). A significant (P<0·04) interaction between DRUG and PRE/POST was found using Wilks' Lambda statistic. The MANOVA was followed by separate univariate analyses for each spirometry variable. As demonstrated in Table 2, atropine, on the average, produced bronchodilation. However, as demonstrated in Table 1, this did not occur to a clinically significant extent in many subjects, primarily because of near-normal pretest spirometry values in those subjects on the day of testing.

Also, as shown in Table 3, relative to placebo, atropine significantly decreased both RSA and cardiac interbeat interval (defined as time, in ms, between EKG *r* spikes). The size in decrement of RSA is almost precisely the same as found among normal subjects in a study by Dellinger *et al.*, using the same dose of atropine, at the same period of time after drug-administration (5). The mean decrease in $\hat{V}$ from the former study was 1·8, while in the current study it was 1·5, a nonsignificant and inconsequential difference. Baseline vagal tone was higher in the previous study, however (7·4, *vs.* 6·0 in the present study), presumably because of a somewhat younger age range (19–30).

Discussion

As reflected in the response to parenteral atropine, the relationship between RSA and cardiac vagal tone among asthmatics is similar to that observed among

Table 2 Effects of atropine on spirometric measures

Spirometry variable	*n*	Atropine				Placebo				*F*	(d.f.)*	*P*<
		Pre		Post		Pre		Post				
		M	SD	M	SD	M	SD	M	SD			
FEV_1	18	2·28	0·84	2·49	0·79	2·32	0·71	2·29	0·79	8·57	(1,17)	0·01
FEV_1/FVC	17	62·5	13·9	70·4	15·2	65·4	11·7	67·1	11·6	6·20	(1,16)	0·03
FEF_{50}%	18	2·17	1·61	2·70	1·74	1·92	1·08	2·00	1·06	3·82	(1,17)	0·07

*The *F* ratios are for the Drug by Pre/Post interaction.

Table 3 Effects of atropine on cardiac vagal tone and cardiac interbeat interval

Measure	*n*	Atropine				Placebo				*F*	(d.f.)*	*P*<
		Pre		Post		Pre		Post				
		M	SD	M	SD	M	SD	M	SD			
$\hat{V}$†	12	6·16	1·39	4·59	2·07	5·56	1·29	6·00	1·41	8·21	(1,22)	0·01
IBI‡	12	806	129	725	126	756	80	791	90	13·05	(1,22)	0·002

**F* ratios are for the Drug × Pre/Post interaction.
†Porges' $\hat{V}$ represents the amplitude of respiratory sinus arrhythmia, a measure of vagal tone. It is expressed as $\log_3$ ms (2).
‡Cardiac interbeat intervals are expressed in ms.

normal subjects. While baseline RSA was lower in the present study, the decrease in RSA following atropine was almost precisely the same as that observed by Dellinger *et al.* (5) among a group of normal subjects, at the same dosage. In both studies, subjects were tested at the same interval after administration of the drug. In this study, as in the study by Dellinger *et al.*, only partial vagal blockade was obtained at this dose. It would be expected that a higher dose would produce complete blockade, as has been shown in the previously published literature. (Because of the discomfort and risks involved in complete vagal blockade, we decided not to use a higher dose in the current study.) The pattern of correlations between expiratory flow rates and RSA demonstrate that changes in flow rates produced by atropine were related to changes in vagal tone, as reflected in RSA. The data also show that initial degree of airway obstruction did not affect this relationship.

The results of this study therefore indicate that the relationship between vagal tone and RSA is not affected by the presence of asthma. This supports the validity of RSA as an index of vagal tone in the asthmatic population. Further examination of dose-dependent changes would be needed to determine whether, as in normal subjects, RSA can precisely predict variations in vagal tone among asthmatics. Because of the noninvasiveness of RSA and its ease of measurement, such work is warranted.

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